Pergamon

PII: S0042-6989(97)00033-3

Vision Res., Vol. 37, No. 16, pp. 2295–2301, 1997

Printed in Great Britain
0042-6989/97 $17.00 + 0.00

Comparison of Red–Green, Blue–Yellow and Achromatic Losses in Glaucoma

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Received 21 June 1996; in revised form 15 January 1997

Achromatic losses in glaucoma would be expected to be greater than, or equal to, red–green chromatic losses if the following assumptions are made: (1) the function of the remaining axons is either unchanged or non-selectively reduced; (2) red–green chromatic information is signaled by the midget ganglion cell system; and (3) the function of the magnocellular system is reduced at least as much as that of the midget ganglion cells. This prediction was tested by measuring red–green (along with blue–yellow) mixture thresholds for 1 deg, 0.2 sec test spots presented on a color monitor on a white background of 50 cd/m^2. Ellipses were fitted to plots of green contrast as a function of red contrast (or yellow as a function of blue), and major and minor axes of these ellipses were taken as measures of chromatic and achromatic thresholds, respectively. The study population consisted of 29 eyes in 29 patients with early glaucoma; control data were derived from a data bank of 83 normal eyes. Red–green losses were significantly ($P < 0.05$) greater than achromatic losses in 6 out of the 11 eyes which showed significant losses of either chromatic or achromatic sensitivity (or both). It is concluded that, for these eyes, at least one of the above three assumptions is incorrect. © 1997 Elsevier Science Ltd.

Glaucoma red–green sensitivity Achromatic sensitivity Magno Parvo

INTRODUCTION

There is considerable interest in interpreting the selectivity of visual loss in glaucoma in terms of preferential losses of different types of axon in the optic nerve. For example, there is evidence that large axons and ganglion cells are more affected than small ones (Quigley *et al.*, 1988, 1989) so this may be the basis of some selective changes in visual sensitivity in glaucoma, such as the relatively large reduction in sensitivity to high frequency flicker (Tyler, 1981). To interpret visual sensitivity measurements in glaucoma in terms of changes in different types of axons, we believe it is important to state explicit hypotheses about the changes in function of retinal ganglion cells which may occur in glaucoma, as well as to specify models of the role of these ganglion cells in transmitting different types of visual information.

The loss of visual sensitivity which occurs in glaucoma is typically accompanied by extensive loss of optic nerve axons (Quigley *et al.*, 1982). Given this fact, the following two alternative hypotheses for the observed loss in sensitivity may be proposed:

1. The "Loss-only" hypothesis. The simplest form of this hypothesis is that loss of sensitivity is due *entirely* to the loss of axons, whereas the remaining axons still retain normal sensitivity and performance. Slightly different versions of this hypothesis are that some affected axons might still be present anatomically, but they have either (1) lost the ability to respond to visual stimuli entirely; or (2) lost sensitivity non-selectively (so that, for example, the sensitivity of a ganglion cell to flicker would be reduced by the same factor at all frequencies). Visual performance in all three versions of this hypothesis would presumably be very similar. According to the "Loss-only" hypothesis, the sensitivity losses in glaucoma would be determined by the relative losses of different cell types in glaucoma and by the visual sensitivity functions of these different cell types.
2. The "Loss/damage" hypothesis. In this hypothesis, visual performance of some or all of the remaining functional ganglion cells may be damaged or altered in a selective manner, so that, for example, sensitivity of a cell may be reduced more at some frequencies than at others. This hypothesis is more complex than the Loss-only hypothesis; sensitivity

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losses in glaucoma would involve not only the relative losses of different cell types, but also knowledge of the abnormal form of visual sensitivity functions of damaged cells. According to the Loss/damage hypothesis, selective changes in visual sensitivity (e.g., at different frequencies) could be due either to selective loss of different types of cell, or selective losses in sensitivity of the remaining cells (or to both these selective losses).

To apply and compare these hypotheses, it is necessary to consider the different types of primate ganglion cells and their visual sensitivity to different stimuli. It is generally agreed that much of the achromatic information (e.g., related to rapid motion and flicker) is transmitted by the large cells and axons of the magnocellular pathway (Schiller *et al.*, 1990). There is also a pathway signaling blue–yellow information; this pathway involves medium-sized bistratified ganglion cells (Dacey & Lee, 1994) and probably also other ganglion cells (Klug *et al.*, 1992; D. J. Calkins, personal communication). However, two alternative models for the coding of *red–green* information need to be considered (Rodieck, 1991):

1. In the "Double Duty" model, red–green information is signaled primarily by the red–green opponent, midget ganglion cells which form the major part of the projection to the parvocellular layers of the lateral geniculate nucleus (LGN). These cells have both color and spatial opponency and they have small receptive field centers (Wiesel & Hubel, 1966; de Monasterio & Gouras, 1975). Thus, these cells could potentially perform a double duty, signaling both color and spatial information. According to this model, loss of midget ganglion cells would lead to a loss of both red–green color vision and achromatic sensitivity for spatial detail (Grigsby *et al.*, 1991).
2. In Rodieck's "Two-Channel" model, as in the Double Duty model, an achromatic signal giving spatial detail is derived from the midget ganglion cell system. However, in this model, the red–green color information is provided primarily by another (e.g., bistratified) type of ganglion cell. According to this model, losses of red–green color sensitivity and achromatic spatial detail would correspond to losses in different ganglion cells' systems, and so could occur independently in an optic nerve disorder.

The two hypotheses about sensitivity loss in glaucoma—Loss-only and Loss/damage—and the two models of visual signal transmission— Double Duty and Two-Channel—may be combined in various ways to make testable predictions about visual sensitivity loss in glaucoma. For example, consider that one accepts both the Loss-only hypothesis and the Double Duty model. Evidence suggests that glaucoma preferentially affects both the magnocellular pathway (Quigley *et al.*, 1988, 1989) and the blue–yellow pathway (Sample *et al.*, 1986; Kalloniatis *et al.*, 1993; Johnson *et al.*, 1993). On the Double Duty model, the remaining pathway—the red–green midget system—is presumably relatively unaffected; the following argument shows that there should be a relative sparing of red–green color sensitivity. Consider a comparison of red–green and achromatic sensitivity under the same experimental conditions (e.g., state of adaptation and stimulus location, size and duration). Suppose first that the detection of the achromatic stimulus is performed mainly by the magno system; then if the magno system is more affected than the red–green midget system in glaucoma, achromatic sensitivity should be reduced more than the red–green sensitivity. Alternatively, suppose that achromatic detection is performed mainly by the achromatic (spatial detail) signal from the parvo system; in this case, red–green and achromatic sensitivity should both be reduced about equally. In either case, it is predicted that the loss of red–green sensitivity should not be greater than the loss of achromatic sensitivity. It should be noted that the other "hypotheses" and "models" do not necessarily lead to this prediction. Thus, on the Two-Channel model, a preferential loss of the (bistratified?) red–green ganglion cells could cause a selective loss of red–green color sensitivity when compared to achromatic sensitivity derived from the midget (spatial detail) system. On the Loss/damage hypothesis, a selective loss of red–green sensitivity (compared to achromatic sensitivity) could be explained by a change in the properties of the red–green midget cells—e.g., they may tend to lose their color-opponency but still retain sensitivity to achromatic stimuli.

The principle aim of the current studies is to compare losses of red–green chromatic and achromatic sensitivity for foveal vision in glaucoma. If red–green sensitivity losses are found to be significantly more than achromatic losses in a sizable number of patients, this would indicate that at least one of the following common assumptions is incorrect for these patients:

1. The Loss-only hypothesis.
2. The Double Duty model.
3. The assumption that the loss of function of the magnocellular system is greater than the loss of function in the (red–green) midget system (at least for foveal vision).

MATERIALS AND METHODS

Chromatic and achromatic thresholds

Color mixture thresholds were measured with the technique and equipment described by Grigsby *et al.* (1991). Briefly, 1 deg, 0.2 sec circular test spots were presented foveally, superimposed on a white background of 50 cd/m^2, on a color video display. Each test stimulus was a mixture of two color "primaries"—either red and green or blue and yellow. Each component could be either an increment or a decrement (or zero contrast). Thresholds for each stimulus were determined with a yes–no procedure, using eight trials, based on ZEST, a modified form of the QUEST threshold method (Watson & Pelli, 1983; King-Smith *et al.*, 1994); both red–green

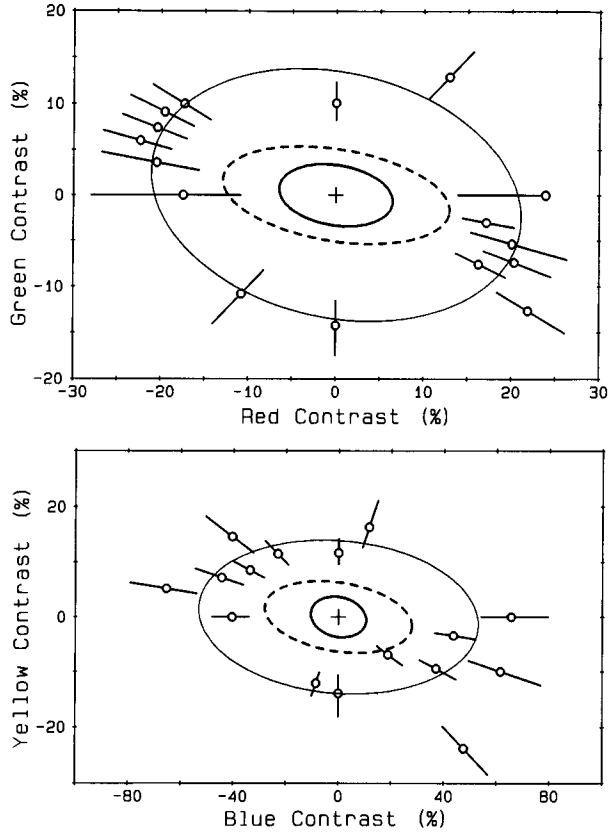

FIGURE 1. Foveal color-mixture threshold plots for the right eye of a 35-yr-old white male with primary open-angle glaucoma. The upper plot shows red–green mixture thresholds. Circles represent the 16 threshold measurements where the contrast (Weber fraction) of the green phosphor is plotted as a function of the contrast of the red phosphor; positive and negative contrasts correspond to increments and decrements, respectively. Error bars indicate ± 1 standard error of the threshold estimates determined from the ZEST method. The thin solid ellipse has been fitted to these data points by a least squares method (Sellers *et al.*, 1986), whereas the thick solid ellipse corresponds to age-matched normal data; the dashed ellipse has a length and width which correspond to the upper boundary of the 95% confidence range for normal controls. The lower plot correspondingly shows blue–yellow mixture thresholds. The loss of sensitivity (increase in threshold) in this eye is described as "non-selective" in that both the lengths (color thresholds) and widths (achromatic thresholds) of the patient's ellipses are increased by about the same factor above normal, so that the length/width ratios remain in the normal range.

and blue–yellow mixture thresholds were measured simultaneously with random interleaving of stimuli. Results were displayed by plotting the phosphor contrast (Weber fraction) for one component (e.g., green) as a function of the phosphor contrast of the other component (e.g., red—see Fig. 1). These data were then fitted with an ellipse (Sellers *et al.*, 1986). As in previous studies (Sellers *et al.*, 1986; Dain *et al.*, 1990; Grigsby *et al.*, 1991) the length of the ellipse was taken as a measure of chromatic threshold and the width of the ellipse as a measure of achromatic threshold; justification of this interpretation has been discussed previously (Sellers *et al.*, 1986). An advantage of this method is that it automatically compensates for inter-subject differences in sensitivity to the two primaries, e.g. due to absorption in the ocular media (Sellers *et al.*, 1986).

Subjects

Twenty-nine eyes were measured from 29 primary open angle glaucoma patients (mean age 56.3 yr, range 35–79 yr) who were recruited from the Ohio State University Department of Ophthalmology. All glaucomatous eyes had intraocular pressure before treatment greater than 21 mmHg, and had visual field defects consistent with glaucoma as measured by the Humphrey Visual Field Analyzer. All eyes also had glaucomatous appearing optic nerve cupping which correlated well with visual field defects. All eyes had foveal fixation (evaluated with the Propper Ophthalmic Grid). Patients were excluded if they had significant ocular media opacities, if they had other visual disorders, if they were on miotic medication or if they had a congenital color defect demonstrated with the Nagel anomaloscope.

Threshold data (lengths, widths and length/width ratios of the ellipses fitted to red–green and blue–yellow mixture thresholds) from these patients were compared with control data derived from a data bank of 83 normal eyes (one eye per subject); the method of deriving age-matched control data, (gaussian-weighted means), for any age in years, has been described (Grigsby *et al.*, 1991). A corresponding weighted estimate of the standard deviation of the normal population was derived in a similar manner; for statistical testing of whether a patient was within the normal range, a (two-tailed) "modified *t*-test" was developed which takes into account the number of normal controls used for estimating the standard deviation at each age (King-Smith, in preparation).

Normal subjects were classified as having intraocular pressure below 20 mmHg, no pathological cupping or pallor of the optic nerve head, no significant ocular media opacities, no congenital color defect (by Nagel anomaloscope) and no retinal disease by fundus examination. All eyes were corrected for the viewing distance of 200 cm and natural pupils were used. Tinted contact lenses and spectacle lenses were replaced by trial lenses in a trial frame. Informed consent was obtained from all subjects, after the nature and possible consequences of the study were explained; the research followed the tenets of the Declaration of Helsinki and was approved by our institutional human experimentation committee.

RESULTS

Color-mixture thresholds for glaucomatous eyes showed somewhat variable patterns of loss. One type of loss is shown in Fig. 1, for the right eye of a 35-yr-old white male. Upper and lower plots correspond to red–green and blue–yellow mixture thresholds, respectively. Circles represent the patient's thresholds and the thin solid ellipses have been fitted to these data points; the thick solid ellipses are age-matched normal control data, and the dashed ellipses have lengths and widths which correspond to the upper boundary of the 95% confidence interval for normal controls (based on our modified *t*-test, see Methods).

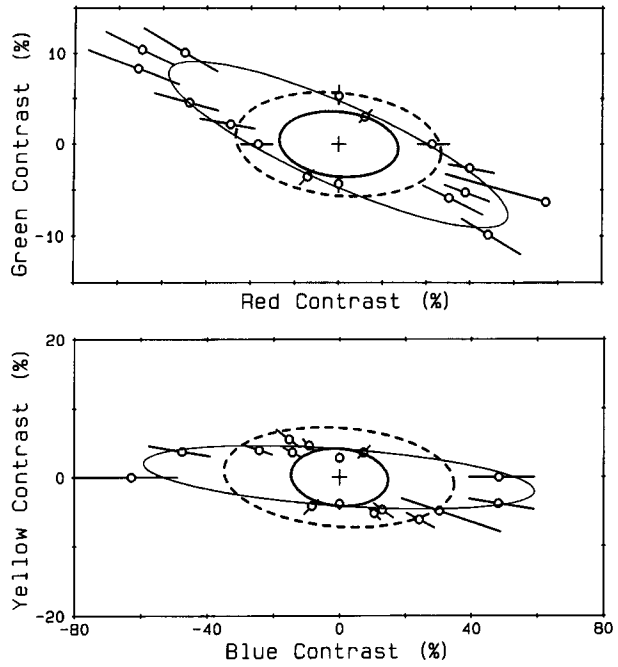

FIGURE 2. Color-mixture thresholds for the right eye of a 47-yr-old white female; for details, see caption of Fig. 1. This eye demonstrates "color-selective" losses in that the lengths (color thresholds) of the fitted ellipses are increased significantly more than the widths (achromatic thresholds).

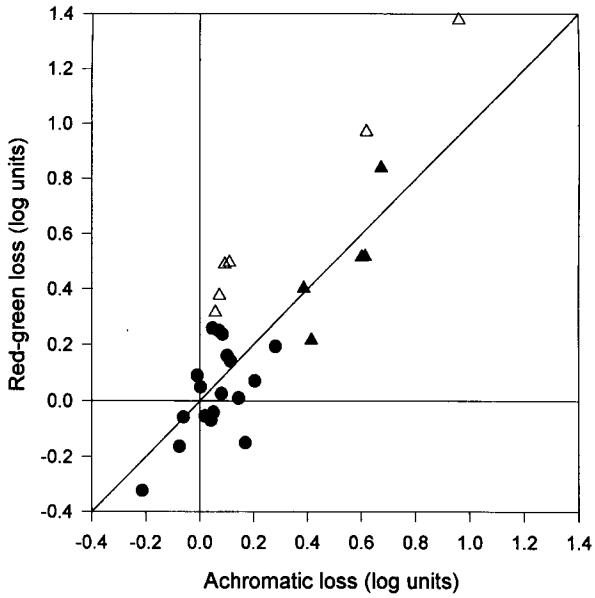

FIGURE 3. Red–green loss (i.e., length of the red–green ellipse divided by age-matched control) plotted against achromatic loss (derived in a similar way from ellipse widths). The diagonal line corresponds to equal losses of red–green and achromatic sensitivity. Triangles represent eyes showing significant losses (above the normal 95% confidence interval for length, width and/or length/width ratio). Open triangles represent selective losses (significantly increased length/width ratio, $P < 0.05$, modified t-test) while filled triangles represent non-selective losses. Filled circles represent eyes which were within the normal range for length, width and length/width ratio.

It is seen that, for both red–green and blue–yellow ellipses, both length (chromatic threshold) and width (achromatic threshold) are significantly increased, being above the 95% confidence interval for normals. The losses are non-selective in that both length and width are increased about equally compared to normal; thus, the patient's length/width (chromatic/achromatic) ratios, 1.59 (red–green) and 3.81 (blue–yellow), were similar to the age-matched normal ratios of 1.93 and 2.85 and within the normal range ($P > 0.05$, modified t-test).

A somewhat different pattern of loss is shown in Fig. 2 for the right eye of a 47-yr-old white female. In this case, the losses are color-selective, for both red–green and blue–yellow ellipses; the lengths are above the 95% confidence interval for normals but the widths are within the normal range. Correspondingly the length/width (chromatic/achromatic) ratios, 4.75 (red–green) and 14.25 (blue–yellow), are greater than age-matched norms—1.92 and 3.53 ($P < 0.002$ and $P < 0.001$, respectively, for red–green and blue–yellow, modified t-test); thus, chromatic thresholds are increased significantly more than achromatic thresholds.

A summary of the red–green mixture thresholds for all the glaucomatous eyes is given in Fig. 3, where the red–green loss (i.e., ellipse length divided by age-matched normal length, expressed in log units) is plotted against the achromatic loss (derived in a similar way from ellipse widths). The diagonal line represents equal red–green and achromatic losses, so points above this line represent eyes whose red–green losses are greater than achromatic losses. Triangles represent eyes showing significant losses ($P < 0.05$, modified t-test, for length, width and/or length/width ratio); six open triangles represent selective losses (significantly increased length/width ratios, $P < 0.05$, modified t-test) while five filled triangles represent non-selective losses (length/width ratios within the normal range, $P > 0.05$). Filled circles represent eyes which were within the normal range for length, width and length/width ratio.

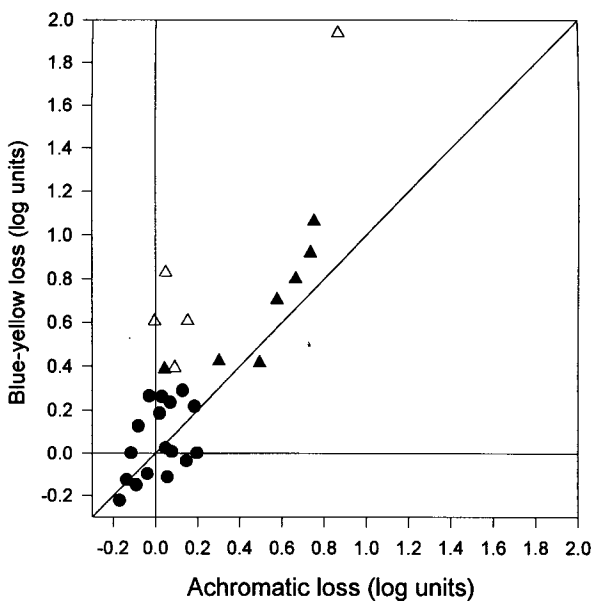

FIGURE 4. Blue–yellow loss plotted against achromatic loss. For details, see caption to Fig. 3.

A similar summary of blue–yellow mixture thresholds is given in Fig. 4. In this case, five eyes (open triangles) gave selective losses, whereas seven eyes (filled triangles) gave non-selective losses.

DISCUSSION

Figure 3 illustrates the main result of our studies, namely that red–green chromatic sensitivity was significantly more affected than achromatic sensitivity in six out of the 11 glaucomatous eyes which showed any significant loss for red–green mixture thresholds (either chromatic or achromatic loss or both). The probability of obtaining, by chance, six or more significantly ($P < 0.05$) selective losses out of 11 is less than 0.001 (derived from the binomial distribution).

Although there has been more interest in selective losses of blue–yellow sensitivity (as in Fig. 4) there have been a few previous reports of selective red–green losses. Red–green gratings were reported to be superior to blue–yellow and achromatic gratings in demonstrating a significant reduction in amplitude of the pattern ERG in glaucomatous eyes (Korth & Horn, 1990), and red–green flicker may be better than blue–yellow flicker at detecting sensitivity loss in suspects (Brussell *et al.*, 1989). Kalloniatis *et al.* (1993) report that in the advanced stage of experimental glaucoma, the red–green opponent mechanism may be more affected than other cone and rod pathways. Greenstein *et al.* (1996) reported red–green losses which were greater than achromatic losses in primary open angle glaucoma (but not in pigmentary glaucoma) but they did not report whether this difference was statistically significant. Peripheral color losses in ocular hypertension and glaucoma patients are similar along protan, deutan and tritan color axes (Yu *et al.*, 1991); if blue–yellow losses are greater than achromatic losses (e.g. Johnson *et al.*, 1993), this implies that red–green losses should also be greater than achromatic losses. However, it should be noted that some data indicate relatively small red–green losses in glaucoma. Gunduz *et al.* (1988) found that protan and deutan losses were considerably smaller than tritan losses for a centrally viewed, square wave grating; a comparison between red–green and achromatic losses was not performed. Felius *et al.* (1995) report that red–green thresholds were affected about as much as achromatic thresholds for a peripheral stimulus; the discrepancy with our results may be due to stimulus location (peripheral vs foveal) or sampling errors (their 14 early glaucoma patients had relatively mild losses of red–green and achromatic sensitivity).

If it is accepted that foveal red–green sensitivity is more reduced than achromatic sensitivity in at least some glaucoma patients, then at least one of the following three assumptions must be wrong: namely, the Loss-only hypothesis, the Double Duty model or the assumption that loss of magnocellular function is greater than that of red–green midget cells (at least for foveal vision). Each of these assumptions will be considered in turn.

The Loss-only hypothesis

According to the simplest form of this hypothesis, the remaining optic nerve axons in glaucoma have normal visual sensitivities and properties. The most direct test of this hypothesis is probably that of Smith *et al.* (1993) who recorded from retinal inputs and cells in the LGN of monkeys with experimental glaucoma. They found that the characteristics of the remaining cells were either within the normal range or only slightly affected. However, it should be noted that these studies were performed on monkeys with chronic glaucoma at 20–52 months after laser trabeculoplasty; it is possible that greater changes in the properties of the remaining cells would have been observed at an acute stage, soon after the operation. Also, the studies were concerned mainly with spatial properties such as responses to sinusoidal gratings; chromatic and flickering stimuli were not tested.

There have been a number of suggestions which would support the alternative Loss/damage hypothesis that changes in visual function in glaucoma may involve selective changes in response properties of the remaining ganglion cells. Eisner & Samples (1991) present evidence that "profound reduction of flicker sensitivity" in glaucoma can be due to inadequate lateral antagonism, thus depending on retinal dysfunction rather than on optic nerve compromise alone. Additionally, the flicker electroretinogram (ERG) can be considerably reduced in glaucoma (Holopigian *et al.*, 1990); if ganglion cells do not contribute significantly to the flicker ERG (Maffei & Fiorentini, 1981), this implies that losses of sensitivity occur in the inner retina, which could cause selective changes in the properties of individual ganglion cells. A similar conclusion may be derived from the changes in the electrooculogram which have been described in glaucoma and ocular hypertension (Mehaffey *et al.*, 1993). Selective loss of short wavelength cones has been reported in advanced glaucoma (Millechia *et al.*, 1992); such a loss of cones could presumably affect the properties of any surviving blue–yellow ganglion cells. Selective loss of function of the outer extremities of ganglion cell dendrites has been proposed to explain contrast sensitivity measurements (Neima *et al.*, 1984). Large changes in light adaptation have been described in advanced experimental glaucoma by Kalloniatis *et al.* (1993). For example, in one treated monkey eye, the threshold for a red foveal test spot was raised by 4.7 log units at absolute threshold, but only by 1.0 log units when it was presented on a bright green background; this implies that the background had much less effect than normal in raising the threshold for the test spot, and this large change in adaptational properties is difficult to explain using the Loss-only hypothesis (one would need to propose that the remaining cells in the glaucomatous eye had greatly different adaptational properties from the ones used in the normal eye).

The current results could be explained in terms of the Loss/damage hypothesis if color-opponency in the red–green midget cells were reduced in glaucoma. Reid & Shapley (1992) provide evidence that both the center and

surround of the receptive field of this type of cell are derived from a single cone type (e.g., long-wavelength (L) cones in the center, mid-wavelength (M) cones in the surround). If glaucoma caused a loss of specificity in the surround, so that it received input from both L and M cones, sensitivity to chromatic (but not achromatic) stimuli would be reduced. For example, in a red on-center, green off-surround cell, response to an equiluminous red test spot (covering both center and surround) would be reduced by the additional L cone response from the surround; there would be little or no change in the response to an achromatic stimulus.

The Double Duty model

In the Double Duty model, midget ganglion cells signal both spatial detail and red–green color. Rodieck (1991) has proposed, instead, a Two-Channel model in which red–green color is primarily signaled by bistratified ganglion cells. The physiological properties of these cells correspond to the Type II cells of Wiesel & Hubel (1966). Neutral wavelengths for these cells are much less variable than those for the red–green midget cells (Type I) and this may make them more suitable for signaling red–green color information (Rodieck, 1991). On Rodieck's Two-Channel model, the selective losses of both red–green and blue–yellow sensitivity (compared to achromatic sensitivity) would correspond to a selective loss of bistratified ganglion cells compared to other cells—the red–green midget cells and, perhaps, the parasol cells of the magnocellular pathway. Indeed, if glaucoma causes a selective loss of function of bistratified (Type II) ganglion cells, then the Two-Channel model provides an explanation of why the selectivity of red–green (Fig. 3) and blue–yellow (Fig. 4) losses follow similar patterns.

Magnocellular vs parvocellular losses

Quigley and his colleagues have provided extensive evidence for selective loss of large ganglion cells and axons in both monkeys with experimental glaucoma (Dandona *et al.*, 1991; Glovinsky *et al.*, 1993) and human glaucoma (Quigley *et al.*, 1988, 1989). Some psychophysical losses, such as the selective loss of sensitivity at high temporal frequencies (Tyler, 1981) could also be ascribed to a selective loss of the magnocellular system.

However, selective damage to the magnocellular system may not be a universal rule in glaucoma. For example, Quigley's observations were not replicated in the experimental glaucoma of Zamber *et al.* (1988). Smith *et al.* (1993), using single unit recordings from monkeys with experimental glaucoma, did not confirm a selective loss of the magnocellular system, but instead proposed that the largest cells within both magno and parvo systems may be selectively affected. There may also be an important difference between acute and chronic glaucoma. Thus, Dandona *et al.* (1991) found a selective loss of rapid axon transport to the magnocellular layers of the LGN in *chronic* glaucoma, but an *acute* elevation of intraocular pressure affected transport to the parvocellular layers more than to the magnocellular layers. Similarly, Shou & Zhou (1989) found that, in the cat, visual responses from small (X) ganglion cells were more susceptible to raised intraocular pressure than responses from large (Y) cells. Another important distinction may be between foveal and peripheral retina. For example, near the fovea, Quigley *et al.* (1989) did not find the selective loss of large ganglion cell bodies in human glaucoma which was evident in peripheral retina. Similarly, for foveal vision, Dandona *et al.* (1991) did not show the differential blockage of axon transport to magnocellular layers, which they could demonstrate for peripheral vision.

In conclusion, the selective loss of red–green sensitivity observed in some glaucoma patients (e.g., Fig. 2) indicates that at least one of the following is true:

1. The visual characteristics of the remaining ganglion cells are selectively altered.
2. Red–green information is primarily transmitted by bistratified rather than by midget ganglion cells.
3. Loss of midget ganglion cells is greater than the loss of magno (parasol) ganglion cells, at least in some situations (e.g. foveal vision or acute elevation of intraocular pressure).

Our results also indicate that patients may show different patterns of psychophysical loss (e.g., Figs 1 and 2), which may perhaps relate to differences in etiology (e.g. mechanical vs ischemic damage; Hoskins & Kass, 1989).

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Acknowledgements—This work was supported by NIH grant EY 04948 and the Ohio Lions Eye Research Foundation. We thank Drs David Calkins and Earl Smith, III, for their advice and Dr David Leighty, Statistical Consulting Service, the Ohio State University, for statistical advice.